CARDIOVASCULAR EVALUATION

1. Introduction

The effects of Herbicide Orange and its dioxin contaminant on the cardiovascular system are not well defined. Both bradycardia and tachycardia have been suggested in acute heavy exposures to the 2,4-D and 2,4,5-T components, but the cardiovascular effects following chronic low dose exposure are essentially unknown. The thrust of this cardiovascular evaluation has been to collect important data by questionnaire, physical examination, and laboratory testing, that would identify Ranch Hand-comparison group differences after accounting for the effects of confounding variables. Of the well-established risk factors for cardiovascular disease, smoking, cholesterol level or cholesterol to high density lipoprotein (HDL) ratio, and age were selected as covariates in most analyses (Brand et al, 1976). The covariates were categorized as follows: age, ≤ 40, 40 years 1 month - 59 years 11 months (abbreviated 40 < > 60), and 60 years or more; smoking, 0 pack-years, 1-10 pack-years, and 11 or more pack-years; cholesterol, ≤ 180 mg/dl, 181-279 mg/dl, and ≥ 280 mg/dl; and cholesterol-HDL ratio, <5.3, ≥ 5.3. In complex analyses with sparse data, trichotomous covariates were reduced to dichotomous ones. The cutpoint for cholesterol-HDL ratio was derived from data on rated Air Force personnel referred for cardiovascular diagnostic examination; it is an unweighted average of means of flyers verified at cardiac catheterization as having or not having occlusive coronary atherosclerosis. A more optimal approach, based upon a median HDL value of the comparison group, will be used in subsequent reports. Statistically significant interactions between these covariates were not explored in detail when there was no effect on group membership and when the interactions were consonant with the classical epidemiology of cardiovascular disease. Analyses of weak risk factors in the data will be presented in subsequent reports. Because of the low proportion of Black participants in both groups, covariate adjustment by race was not possible. Consequently, a variety of dependent variable analyses by race, unadjusted for age, smoking, and cholesterol, are discussed throughout this chapter. In addition, where adjusted group differences were found to be statistically significant, other covariates (e.g., percent body fat, current smoking, history of intermittent claudication, testosterone level, differential cortisol level, etc.) have been used to reanalyze all data in an attempt to clarify the clinical significance of the finding.

Most analyses herein are based upon Ranch Hand contrasts to the "originals" of the comparison group. Where group associations are statistically significant or of general interest, other comparison group denominators have been used (e.g., matched originals only and the entire comparison group). Further, for specific analyses, participants with diabetes and pedal edema have been deleted. Small denominator fluctuations are also inherent in these analyses because of missing covariate or dependent variable information. Thus, tabular data may not be directly comparable between analyses because of the type of

covariate adjustment, or the denominator of the comparison group, or the deletion of certain medical conditions thought to confound a specific clinical diagnosis. In general, covariates having a nonsignificant association with the dependent variable were removed from the analysis. The statistical analyses are based on log-linear models (BMDP-4F), logistic regression (BMDP-LR), and generalized linear models, chi-square, t tests, and matched covariate analyses (Breslow, 1982). Relative risks and confidence intervals, computed using the hypergeometric distribution (Thomas, 1971) and the normal approximation (Fleiss, 1981), are shown for all dependent variables in Appendix XVIII.

2. Central Cardiovascular System

a. Systolic Blood Pressure

Abnormal systolic blood pressure was defined as pressure in excess of 140 mmHg by standard observer auscultation. All blood pressures were obtained in a sitting position. Second or third readings were recorded on those individuals who manifested an initial elevation. There was no significant difference in systolic blood pressure (P = 0.248) between the non-Black Ranch Hand and the non-Black original comparison group after adjusting for age, smoking, and cholesterol level. These data are reflected in Tables XVI-1-1 and XVI-1-2. Diabetics (2-hour postprandial glucose ≥120 mg/dl) were removed from the analyses.

Table XVI-1-1

SYSTOLIC BLOOD PRESSURE
RANCH HANDERS AND THE ORIGINAL COMPARISONS VERSUS AGE
(NON-BLACKS ONLY)

	Ranch Hand			Original Comparisons			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	36	10.4	309	32	14.3	192	68	11.9	501
≥40	113	23.1	377	94	24.6	288	207	23.7	665

Systolic pressure between groups: P = 0.248   Age versus systolic
Relative risk under 40: .73, 95% Conf int (.46,1.18) pressure (unadjusted
Relative risk over 40: .94, 95% Conf int (.73,1.20) for smoking and chol-
                                                     esterol): P <0.0001

The unadjusted systolic blood pressure by smoking history association, presented in Table XVI-1-2, is not significant (P=0.179) in these data.

Table XVI-1-2

SYSTOLIC BLOOD PRESSURE PARTICIPANTS BY SMOKING HISTORY
(NON-BLACKS ONLY)

Smoking History in Pack-Years	Abnormal	% Abnormal	Normal
0	70	17.8	324
1-10	44	16.1	230
>10	161	20.8	612

P = 0.179

Ranch Handers and original comparisons reflected in these tables were also compared on systolic blood pressure as a continuous variable with adjustment for age, smoking history, HDL ratio, and body fat, via a general linear model. There was no significant difference between the groups on systolic blood pressure (P = 0.976). The Ranch Hand and original comparison adjusted means were 133.12 and 133.15, respectively. The covariates of age and body fat were both significantly associated with systolic blood pressure (P = 0.0001).

Additional categorical analyses comparing Non-Black Ranch Handers with the total non-Black comparison group adjusted for age, smoking, and cholesterol showed comparable nonsignificant intergroup differences (P = 0.366) for systolic blood pressure. The effects of age and smoking were statistically significant, P <0.0001 and P = 0.04, respectively. In addition, a chi-square analysis of Black Ranch Handers and Black individuals from the entire comparison group (diabetics removed) showed no group difference (P = 0.265) in systolic pressure.

b. Diastolic Blood Pressure

Diastolic blood pressure in excess of 90 mmHg was categorized as abnormal. No significant intergroup difference was noted after adjustment for age, smoking, and cholesterol level. These data are based upon non-Black, nondiabetic denominators and are presented in Table XVI-1-3.

Table XVI-1-3

DIASTOLIC BLOOD PRESSURE
IN RANCH HANDERS AND THE ORIGINAL COMPARISONS VERSUS AGE
(NON-BLACKS ONLY)

	Ranch Hand			Original Comparisons			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	18	5.2	327	12	5.4	212	30	5.3	539
≥40	57	11.6	433	53	13.9	329	110	12.6	762

Diastolic blood pressure P = 0.351
between groups:
Relative risk under 40: .97,95% Conf. int. (.45,2.18)
Relative risk over 40: .84,95% Conf. int. (.58,1.21)

Age versus diastolic
pressure (unadjusted
for smoking and chol-
esterol): P <0.0001

    The Ranch Handers and original comparisons (as represented in Table XVI-1-3) diastolic blood pressure was also compared as a continuous variable with adjustment for age, smoking history, HDL ratio, and body fat, via a general linear model. There was a borderline significant diastolic blood pressure by group by age interaction (P = 0.0585), indicating a change in the blood pressure by group association with level of age (<40, ≥40). However, separate analyses at each level of age revealed no significant group differences. In the under-40 age group, the diastolic blood pressure by group association was not significant (P = 0.435); the adjusted group means were 78.2 and 77.02 for Ranch Handers and comparisons, respectively. In the 40-and-over age group, the diastolic blood pressure by group association was not significant (P = 0.904); the Ranch Hand and comparison adjusted means were 80.7 and 81.7, respectively.

    An intergroup log linear analysis of diastolic blood pressure for Blacks and non-Blacks using original comparisons showed comparable nonsignificant results (P = 0.573). Age was a significant covariate (P <0.0001) while the history of past smoking was not. An unadjusted contrast of Black Ranch Handers and Black individuals from the entire comparison group also showed similar nonsignificant group differences (P = 0.533).

    c. Electrocardiograms (ECG's)

    ECG's were obtained on all participants, following a minimum fast of 4 hours and abstinence from tobacco for 4 hours. The vast majority of ECG's were obtained by 1 or 2 technicians on dedicated and calibrated machines. The tracings were read by a contract clinic cardiologist and categorized into normal and abnormal groups, the latter consisting of right bundle branch block, left bundle branch block, nonspecific T wave changes, bradycardia, tachycardia, and

other diagnoses. Grave findings were immediately discussed with the partici-
pant's family physician and appropriate follow-up was arranged. As shown in
Table XVI-1-4, abnormal ECG findings were not associated with group member-
ship (P = 0.987). For both the non-Black Ranch Hand and original comparison
groups, there was a highly statistically significant (P <0.0006) association
between abnormal ECG's and increased age.

Table XVI-1-4

ECG FINDINGS IN RANCH HANDERS AND THE ORIGINAL COMPARISONS
BY AGE, ADJUSTED FOR SMOKING HISTORY AND HDL RATIO
(NON-BLACKS ONLY)

	Ranch Hand			Original Comparisons			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	69	20.1	274	51	23.1	170	120	21.3	444
≥40	148	30.2	342	107	28.4	269	255	29.4	611

Abnormal ECG findings between groups: P = 0.987   ECG findings in both
Relative risk under 40: .87,95% Conf. int. (.62,1.23) groups by age (un-
Relative risk over 40: 1.06,95% Conf. int. (.86,1.32) adjusted for smoking
and HDL ratio):
P = < 0.0006

When the ECG data in Table XVI-1-4 were redistributed into the catego-
ries of tachycardia, bradycardia, other abnormalities, and normal, an unad-
justed analysis showed no significant differences between the Ranch Hand and
original comparison group (P = 0.881).

An additional cardiac assessment was made on all past or present flying
personnel in both groups. Participants' names and social security numbers were
computer matched to the USAF ECG Repository, the world's largest ECG repository
on flying personnel (Lancaster and Ord, 1972; Hiss and Lamb, 1962). Three
hundred and fifty-four Ranch Handers and 282 original comparisons had between
one and 10 previous tracings on file which had been diagnostically coded by
stringent criteria. Accordingly, USAF cardiologists reviewed all 636 physical
examination ECG's (without knowledge of group membership) and coded them by the
standardized USAF criteria. The physical examination ECG was contrasted to the
past ECG's and categorized as no change or degraded (no ECG's were improved in
either group). These data analyzed by group membership and age are shown in
Table XVI-1-5. Blacks and diabetics were removed from the analysis. This
analysis is not adjusted for elapsed time between ECG readings.

Table XVI-1-5

CLINICAL COMPARISON OF CURRENT ECG'S TO PAST ECG'S IN FLYING PERSONNEL
BY GROUP MEMBERSHIP AND AGE
(NON-BLACKS ONLY)

	Ranch Hand			Comparison			Total		
	No Change	Degraded		No Change	Degraded		No Change	Degraded	
Age	Number	Number	Percent	Number	Number	Percent	Number	Number	Percent
<40	45	2	4.2	29	2	6.4	74	4	5.1
≥40	226/271	20/22	8.1	182/211	17/19	8.5	408/482	37/41	8.3

Because of sparse data in the under-40 age group, an analysis adjusted for both age and smoking was not possible; the unadjusted ECG change by group association was not significant (P = 0.652). In the 40-and-over age group, the ECG change by group association was not significant (P = 0.939), adjusted for smoking history. The smoking history covariate was borderline significant, P = 0.0852. In both the Ranch Hand and comparison groups combined, the age by ECG association (P = 0.412) was not significant. The unadjusted ECG change by smoking history association was significant (P = 0.018).

An overall analysis of systolic/diastolic blood pressures and ECG abnormalities was performed by group membership and adjusted for smoking (0, 1-10, >10 pack-years), cholesterol-HDL ratio (<5.3, ≥5.3), age (<40, ≥40) and differential cortisol level (continuous); Blacks and diabetics were omitted. The differential cortisol level is defined as the 7:30 AM cortisol measurement minus the 9:30 AM cortisol measurement. A logistic regression analysis showed similar nonsignificant results (as in Sections a-c above) that are presented in Table XVI-1-6.

Table XVI-1-6

RANCH HAND AND ORIGINAL COMPARISON GROUP CONTRAST FOLLOWING ADJUSTMENT
FOR AGE, SMOKING, CHOLESTEROL-HDL RATIO, AND DIFFERENTIAL CORTISOL RESULTS
(NON-BLACKS ONLY)

Dependent Variable	P Value
Systolic Blood Pressure	0.195
Diastolic Blood Pressure	0.351
ECG Abnormality	0.999

d. Heart Sounds

All valvular sound abnormalities were recorded following detailed auscultation. Fourth heart sounds were considered abnormal. If the participant indicated that the heart sound abnormality was a new finding, the diagnostician confirmed the abnormality. A review of the heart sound abnormalities in the non-Black Ranch Handers and original comparisons revealed that the data were too sparse for a fully adjusted analysis. An unadjusted group comparison was nonsignificant (P = 0.414), as was the unadjusted effect of age (P = 0.375). Similarly, an unadjusted analysis of Black Ranch Handers and comparison individuals did not demonstrate statistical significance (P = 0.799). A combined race and fully adjusted (age, smoking, cholesterol level) analysis of Ranch Handers and the entire comparison group is presented in Table XVI-1-7. These data also show no group differences (P = 0.592) but do reflect a significant association of heart sound abnormalities and increasing age (P <0.002).

Table XVI-1-7

HEART SOUND ABNORMALITIES
IN BLACK AND NON-BLACK RANCH HANDERS AND ALL COMPARISONS BY AGE

	Ranch Hand			Comparison			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
≤40	5	1.3	367	8	1.9	417	13	1.6	784
40<>60	11	2.3	476	15	2.7	542	26	2.5	1018
≥60	2	11.1	16	2	8.3	22	4	9.5	38

Abnormal heart sounds between groups: P = 0.592   Heart sound abnormalities in both groups by age: P < 0.002

3. Peripheral Cardiovascular System

The status of the peripheral cardiovascular system was evaluated by ophthalmoscopic examination of the eyegrounds for arterial-venous nicking and hemorrhages, auscultation of the carotid arteries, and bilateral palpation for the presence and quality of 5 peripheral pulses. The finding of a bilateral abnormality (e.g., bruits in both carotid arteries) was scored as 1 abnormality. Diminished or absent peripheral pulses were both designated as abnormal. While there is clearly recognized misclassification of the specific causes for the examination findings, it is judged to be of a minor nature; thus, the examination findings are deemed to be generally indicative of the presence

or absence of severe arteriosclerosis. Abdominal x-rays to confirm the severity of the peripheral vessel arteriosclerosis were not obtained because of the possible impact of detected asymptomatic or clinically irrelevant kidney stones upon the flying status of active pilots.

a. Eyegrounds

Abnormal funduscopic findings were not associated with group membership (P = 0.965), but were highly correlated with increased age (P < 0.0001), as reflected in Table XVI-1-8. The additional covariates of smoking history and cholesterol-HDL ratio were nonsignificant in the analysis.

Table XVI-1-8

FUNDUSCOPIC ABNORMALITIES
IN RANCH HANDERS AND ORIGINAL COMPARISONS BY AGE
(NON-BLACKS ONLY)

Age	Ranch Hand			Comparison			Total Both Groups		
	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	8	2.3	333	6	2.7	214	14	2.5	547
≥40	42	8.7	441	31	8.4	339	73	8.6	780

Funduscopic abnormalities between groups: P = 0.965
Relative risk under 40: .86,95% Conf. int. (.26,2.97)
Relative risk over 40: 1.04,95% Conf. int. (.65,1.67)

Funduscopic abnormalities in both groups by age (unadjusted for smoking and cholesterol-HDL ratio) P <0.0001

An unadjusted contrast of Black Ranch Handers and Black individuals from the entire comparison group showed similar nonsignificant results (P = 0.860).

b. Carotid Bruits

The prevalence of carotid bruits in both groups combined was 1.47%. Because of sparse data, an unadjusted analysis comparing non-Black Ranch Handers with non-Black original comparisons was performed; the group by carotid bruits association was nonsignificant (P = 0.269), as was the unadjusted age by carotid bruits association (P = 0.353). However, the larger analysis of both Black and non-Black Ranch Handers with the entire comparison group showed a group membership association of interest (P = 0.183) and a significant relationship between bruits and increasing age (P = 0.03).

c. Peripheral Pulses

The absence or diminished quality of 5 peripheral pulses was determined by detailed clinical palpation. One or more abnormal pulses were found in 12.8%(106/829) of the non-Black Ranch Handers as contrasted to 9.4% (56/596) in the non-Black original comparisons (P = 0.05) giving an unadjusted relative risk of 1.36 with a 95% confidence interval (.99, 1.88). The reader is referred to Appendix XVIII for complete relative risks and confidence intervals. Data on specific pulses are presented in Table XVI-1-9. The covariates of cholesterol-HDL ratio and percent body fat (<25%, ≥25%) were noncontributory in all of the analyses. Thus, the pulse variables were adjusted for age (<40, ≥40) and smoking (0, 1-10, >10 pack-years). Blacks, diabetics, and individuals with peripheral pitting edema were omitted from the analysis. Since most abnormalities were concentrated in the over 40 and > 10 pack-year group, these data were re-analyzed on that subset with the results shown in column three of Table XVI-1-9.

Table XVI-1-9

SUMMARY OF PERIPHERAL PULSE QUALITY:
RANCH HANDERS AND ORIGINAL COMPARISONS
(NON-BLACKS ONLY)

Pulse Examined, Number of Participants	Unadjusted P Value and Direction of Group Abnormalities	Unadjusted P Value for Age ≥40 Years and >10 Pack-Years	Unadjusted P Value Age Versus Pulse (Groups Combined)
Radial N = 1414	0.147 (RH > C)	Sparse Data	0.668
Femoral N = 1414	0.147 (RH > C)	0.117 (RH > C)	0.157
Popliteal N = 1414	0.0255 (RH > C)	0.0159 (RH > C)	0.0065
Dorsalis Pedis N = 1413	0.0644 (0.0406)* (RH > C)	0.0375 (RH > C)	0.0003
Posterior Tibial N = 1413	0.312 (0.250)* (RH > C)	0.123 (RH > C)	0.0022

*Adjusted for age and smoking

Although only two pulses reached statistical significance (P ≤0.05) in Table XVI-1-9, the consistent directional findings in all peripheral pulses were sufficient to merit additional clarifying analyses. Further, these directional findings were present after accounting for diabetes and the clinically confounding physical effects of peripheral pitting edema and obesity. Accordingly, various aggregates of pulses were constructed to determine more precisely the anatomic patterns of the abnormalities. This approach, adjusted by age and smoking history, is displayed in Table XVI-1-10.

Table XVI-1-10

SUMMARY OF PERIPHERAL PULSE ABNORMALITY COMBINATIONS:
RANCH HANDERS AND ORIGINAL COMPARISONS
ADJUSTED BY AGE AND SMOKING HISTORY
(NON-BLACKS ONLY)

Pulse Abnormalities Combination	Adjusted P Value and Direction of Group Abnormalities	Unadjusted P Value Age Versus Pulse Combination
Leg Pulses* (Femoral, Popliteal, Dorsalis Pedis, Posterior Tibial)	0.0302 (RH > C)	0.0001
All Pulses (Carotid, Femoral, Radial, Popliteal, Dorsalis Pedis, Posterior Tibial)	0.0257 (RH > C)	0.0005
Peripheral Pulses (Radial, Femoral, Popliteal, Dorsalis Pedis, Posterior Tibial)	0.0235 (RH > C)	0.0002

*In nondiabetic, non-Black, Ranch Handers and the original comparisons, leg pulses were associated with a history of intermittent claudication (P = 0.0113), and this association was the same in both groups (P = 0.962).

The data in Table XVI-1-10 did not point to specific anatomic groupings but rather suggested a generalized phenomenon. As a result of this finding, the pulse data were reanalyzed using testosterone and differential cortisol results as new covariates. No substantial change in the significance of the pulse findings was observed. In order to provide a complete approach to the peripheral pulse findings, 2 supplemental contrasts using other denominators were performed: 1) an analysis of both Black and non-Black Ranch Handers versus Black and non-Black comparisons from the entire comparison group, adjusted for

age, smoking history in pack-years, and cholesterol level; and 2) an unadjusted analysis of Black Ranch Handers versus Black comparisons from the entire comparison set. The data from these analyses are presented in Table XVI-1-11.

Table XVI-1-11

SUMMARY OF PERIPHERAL PULSE QUALITY:
ALL RANCH HANDERS VERSUS ALL COMPARISONS*, ASSOCIATION OF AGE,
UNADJUSTED CONTRAST OF BLACK RANCH HANDERS AND BLACK COMPARISONS

| Pulse Examined, Number of Participants | Blacks and Non-Blacks | | Blacks Only |
	P Value and Direction of Group Abnormalities	P Value of Age Association Both Groups**	Unadjusted P Value
Radial N = 1884	0.047 (RH > C)	0.012	0.890
Femoral N = 1882	0.134 (RH > C)	0.007	0.219
Popliteal N = 1883	0.0174 (RH > C)	<0.001	0.219
Dorsalis Pedis N = 1881	0.006 (RH > C)	<0.001	0.789
Posterior Tibial N = 1882	0.067 (RH > C)	<0.001	0.557

*Adjusted for age, smoking, and cholesterol level
**Unadjusted for smoking and cholesterol

The data in Table XVI-1-11 are thus corroborative of diminished pulse quality in the Ranch Hand group. These data also weakly suggest that the Ranch Hand - comparison pulse differences may be aggregated in the non-Black population (or may be spurious due to small sample size). A matched pair analysis (matching variables: age, job, race) of data sets for 3 pulses (see Table XVI-1-9), adjusting for percent body fat and smoking history, are shown in Table XVI-1-12. Due to sparse data, only main effects were included in these analyses.

Table XVI-1-12

MATCHED PAIR ANALYSIS FOR THREE PERIPHERAL PULSES:
RANCH HANDERS VERSUS ORIGINAL COMPARISONS
(NON-BLACKS ONLY)

Pulse Variables	P Value and Direction of Group Abnormalities
Popliteal Pulse	0.053 (RH > C)
Dorsalis Pedis	0.050 (RH > C)
Posterior Tibial	0.081 (RH > C)

Thus, the data in Table XVI-1-12 reaffirm the overall finding of significant peripheral pulse deficits in the Ranch Hand group.

4. Risk Factors in Central and Peripheral Cardiovascular Disease

This section emphasizes cardiovascular disease relationships that are highlighted by significant risk factors or combinations of risk factors identified in the preceding sections or in the general literature.

a. Cholesterol and HDL Cholesterol

Nondiabetic non-Black Ranch Handers and the non-Black original comparisons were contrasted for continuous cholesterol and HDL levels via a general linear model, adjusting for age (<40, ≥40), smoking history (0, 1-10, >10 pack-years), and body fat (<25%, ≥25%). Although no group membership differences were found for cholesterol and HDL, several of the covariates were of profound influence. These data are shown in Table XVI-1-13.

Table XVI-1-13

CHOLESTEROL AND HDL IN
RANCH HANDERS AND ORIGINAL COMPARISONS
(NON-BLACKS ONLY)

Dependent Variable	Adjusted Ranch Hand - Comparison P Value	Covariate P Values		
		Age	Smoking	Body Fat
Cholesterol	0.355	0.038	0.002	0.919
HDL	0.178	0.788	0.028	0.0001

Similar results were found in the contrast of nondiabetic Blacks. Because of small sample size, covariate adjustment was not possible. The contrasts were made by t tests and the results are shown in Table XVI-1-14.

Table XVI-1-14

CHOLESTEROL AND HDL RESULTS IN
RANCH HANDERS AND ORIGINAL COMPARISONS
(BLACKS ONLY)

	Ranch Hand			Comparison			
	N	Mean	Standard Deviation	N	Mean	Standard Deviation	P Value
Cholesterol	49	214.3	34.6	37	209.8	41.3	0.595
HDL	49	55.5	17.2	37	52.4	14.6	0.375

b. Age, Past Smoking, Current Smoking Risk Factors

Several analyses have shown the substantial effects of age and smoking on the cardiovascular system. Because of the unknown influence of antismoking campaigns in recent years on Air Force personnel, the covariate of smoking history (0, 1-10, >10 pack-years) may not be fully appropriate, particularly if smoking ceased several years before the examination. Consequently, all dependent variables were reanalyzed for group differences restricting to older (>40), heavy past smokers (>10 pack-years), adjusted for current smoking (yes, no). These contrasts are presented in Table XVI-1-15. Blacks and diabetics were removed for the analysis.

Table XVI-1-15

RANCH HANDERS AND ORIGINAL COMPARISONS
ADJUSTED FOR CURRENT SMOKING
(NON-BLACKS, $\geq$ 40 YEARS, > 10 PACK YEARS ONLY)

Dependent Variable(s)	P Value and Direction of Group Significance	
Systolic Blood Pressure	0.571	
Diastolic Blood Pressure	0.350	
ECG Abnormalities	0.322	
Heart Sound Abnormalities	0.833	
Eyegrounds	0.628	
Carotid Bruits	0.026	RH > C
Radial Pulse	0.258	
Femoral Pulse	0.033	RH > C
Popliteal Pulse	0.001	RH > C
Dorsalis Pedis Pulse	0.002	RH > C
Posterior Tibial Pulse	0.054	RH > C
All Pulses	0.002	RH > C
Leg Pulses	0.003	RH > C

These specific data, when compared to the broader previous analyses in Table XVI-1-9, show decreasing P values. In addition, there is a suggestion that the peripheral pulse deficits are targeted in the older heavy smokers who are currently still smoking.

c. Reported and Verified Heart Disease

All participants were asked 2 questions during the in-home interview that were intended to capture a history of heart disease. The questions were: "Did you ever have a heart condition?" and "Did you ever have any other major health condition?" All affirmative responses were medically coded by the International Classification of Diseases, 9th Edition, Clinically Modified (ICD CM). Twenty-seven distinct cardiac classifications were identified for the Ranch Hand group and 19 were found in the comparison group. Medical records were sought on all of these individuals in order to verify the reported conditions. Table XVI-1-16 summarizes the verification results for the specific question on past heart disease.

Table XVI-1-16

MEDICAL RECORD VERIFICATION OF REPORTED HEART DISEASE

	Ranch Hand Group	Original Comparison Group
Number of reported cardiac conditions	139	98
Medical Records Reviewed	117	81
Medical Records Pending	-22	-17
% Cardiac Conditions Verified	82.9	85.2
% Cardiac Conditions Unsupported	17.1	14.8

Overall, these data show a high confirmation proportion of reported cardiac conditions. Since Table XVI-1-16 does not include results from the second overlapping question (Other major conditions?) and since individuals may have multiple heart disease responses, the following analyses have different numerators and denominators.

All Ranch Handers (diabetics, Blacks, edemics included) were contrasted to the original comparisons for reported heart disease and reported heart attacks. This analysis was supplemented by an analysis on verified heart disease and heart attacks; all these data are summarized in Table XVI-1-17. The unadjusted relative risk and 95% confidence interval for verified heart disease are 1.00 and (.79, 1.27).

Table XVI-1-17

RANCH HAND AND ORIGINAL COMPARISON GROUPS
VERSUS REPORTED AND VERIFIED HEART DISEASE AND HEART ATTACKS

Heart Disease Parameter	Ranch Hand Yes	No	Comparison Yes	No	P Value
Reported Heart Disease	181	864	136	637	0.878
Reported Heart Attack	10	1035	4	769	0.296
Verified Heart Disease	147	898	109	664	0.982
Verified Heart Attack	7	1038	3	770	0.432

While the lack of group differences in Table XVI-1-17 is of interest, and the good agreement between subjective responses and medically verified responses is notable, additional covariate analyses were conducted to rule out any hidden effect of a risk factor interaction that might be associated with group membership. Thus, Ranch Handers and their comparisons were again contrasted for reported heart disease and verified heart disease, adjusting for the covariates of age, smoking, body fat or HDL. As age was confounding for both reported and verified disease, the analyses are age specific. Further, there are significant interactions between smoking, group membership, and disease; these findings are shown in Table XVI-1-18.

Table XVI-1-18

RANCH HAND AND ORIGINAL COMPARISON GROUP:
COVARIATE ANALYSES OF REPORTED AND VERIFIED HEART DISEASE

Parameter and Covariates	Adjusted Intergroup P Value and Direction of Association	
Reported Heart Disease:*		
Body Fat, smoking <40	0.530	(RH = C)
**≥40, less than 10 pack-years	0.0038	(RH < C)
≥40, greater than 10 pack-years	0.139	(RH = C)
Verified Heart Disease*		
HDL, smoking <40	0.506	(RH = C)
***≥40, less than 10 pack-years	0.008	(RH < C)
≥40, greater than 10 pack-years	0.0712	(RH > C)

*Age confounding variable
**Group - heart disease - smoking interaction: P = 0.0054
***Group - heart disease - smoking interaction: P = 0.0047

These data, in contrast to Table XVI-1-17, demonstrate associations of significance. Young Ranch Handers are equivalent to their young comparisons for both reported and verified heart disease; whereas, the older Ranch Handers smoking more than 10 pack-years are manifesting more verified heart disease than their counterparts. Conversely, older Ranch Handers smoking less than 10 pack-years are faring significantly better than their comparisons for both reported and verified heart disease. These associations, in light of essentially negative blood pressure and ECG findings at the physical examination,

could be speculatively attributed to a wide array of post hoc explanations: e.g., a true disease process that will evolve more clearly in the future, an enigmatic finding akin to the peripheral pulse deficits, chance, etc.

d. Cardiovascular Examination Findings and Verified Historical Heart Disease

The cardiovascular examination findings were contrasted to the history of cardiovascular disease as verified by detailed medical record review. The purposes of this analysis were to determine the degree of positive correlation between the examination and the past medical history, and to determine if peripheral pulse abnormalities were associated with known cardiovascular disease. These data are presented in Table XVI-1-19.

Table XVI-1-19

ASSOCIATION OF CENTRAL AND PERIPHERAL CARDIOVASCULAR ABNORMALITIES WITH
VERIFIED HEART DISEASE BY AGE: RANCH HANDERS
VERSUS ORIGINAL COMPARISONS*
(NON-BLACKS ONLY)

Dependent Variable	P Value (Unadjusted) Dependent Variable Versus Verified Heart Disease	P Value (Adjusted for Age) Ranch Hand VersusComparison
Systolic Blood Pressure	<0.00001	0.229
Diastolic Blood Pressure	<0.00001	0.391
Electrocardiogram	<0.00001	0.875
Heart Sounds	0.292	0.316
Carotid Bruits	0.084	0.223
Radial Pulse	0.023	0.152
Femoral Pulse (≥ 40)	0.147	0.104
Posterior Tibial Pulse (>40)	0.103	0.082
Popliteal Pulse (≥ 40)	0.074	0.022
Dorsalis Pedis Pulse (≥ 40)	0.002	0.094
All Pulses (<40)	0.0004	0.205
(≥40)		0.0691
Peripheral Pulses (<40)	0.0007	0.261
(≥40)		0.048
Leg Pulses (<40)	0.0023	0.369
(≥40)		0.044

*Pitting edema omitted for pulse analyses

Systolic, diastolic blood pressure and ECG abnormalities at physical examination showed exceptionally significant (P $\approx$ 0) associations with medical record histories of cardiac disease, regardless of group membership or age. While moderately positive associations are to be expected, the unusual strength of the associations suggests that very few new cases of hypertension or ECG abnormalities were diagnosed at examination, reflecting perhaps, up-to-date medical records due to the overall medical sophistication and free access to medical care by most members of both groups. The association of carotid bruits and previously diagnosed cardiovascular disease was marginally positive but based upon small numbers. Table XVI-1-19 was most revealing for the peripheral pulse abnormalities. For the radial pulse, the data were too sparse for age adjustment but for all other pulse abnormalities, age was confounding, primarily due to a relative lack of abnormalities in the under-40 age group. A remarkably consistent observation in the 40-and-older age group was that significant or borderline significant Ranch Hand - comparison differences were found almost exclusively in those individuals without a history of cardiovascular disease. This uniform pattern is best exemplified by the popliteal pulse data, as shown in Table XVI-1-20.

Table XVI-1-20

ASSOCIATION OF POPLITEAL PULSE ABNORMALITIES
WITH VERIFIED HISTORY OF CARDIOVASCULAR DISEASE BY AGE AND GROUP MEMBERSHIP*

History of Cardiovascular Disease	Group Membership	Popliteal Pulse Findings in $\geq$40 Age Group	
		Abnormal	Normal
Yes (Verified by	Ranch Hand	2	68
record review)	Comparison	2	59
No	Ranch Hand	11	404
	Comparison	0	313

Popliteal pulse by disease history: P = 0.074
Popliteal pulse by disease by group interaction: P = 0.022

*No pulse abnormalities in <40 group

Interpretation of this intriguing finding at the baseline physical examination is not clear. The fact that the abnormal pulses, regardless of group membership, are associated with increased age, heavy past smoking, current smoking (and possibly race), and verified past heart disease and are largely substantiated by the use of 3 related denominators suggest that the finding is real rather than spurious. While there was most likely a tendency to diagnose additional abnormal pulses, given the first abnormal pulse, this

possible examination bias would not likely aggregate in the Ranch Hand group (because of the blind examination) nor in individuals without a history of prior cardiovascular disease. The speculative interpretation of concern is that the finding of substantial "subclinical" peripheral pulse abnormalities (i.e., without a history of past cardiovascular disease) in the Ranch Handers may be a precursor to either clinically manifest arterial disease or central cardiovascular abnormalities. This possibility will receive detailed attention at the first follow-up examination because an analysis of onset times for verified heart disease (adjusted for race, occupation, and age) did not show a significant difference between the Ranch Hand and comparison group ($P = 0.395$). This finding suggests that if the observed pulse abnormalities are a precursor to central cardiovascular disease, this pathogenesis is not manifested by premature heart disease at this time.

5. Exposure Index Analyses

All of the dependent variables within the Ranch Hand group were compared to the exposure index. Systolic and diastolic blood pressure elevations, and ECG, heart sound, and eyeground abnormalities were adjusted for age (<40, ≥ 40). The peripheral pulse analyses were not age adjusted because of sparse data; subjects with peripheral pitting edema were omitted from these comparisons. The exposure index was stratified into 3 categories: low, medium, and high. All analyses were performed on each of 3 occupational categories: officer, flying enlisted, and ground enlisted. This analysis is presented in Table XVI-1-21. Separate age analyses were performed when age was found to be a confounding variable. When some data were too small for valid analysis, the word sparse is written instead of a P value.

Table XVI-1-21

SUMMARY OF EXPOSURE INDEX ANALYSES WITHIN THE RANCH HAND GROUP*

Dependent Variable**	Occupation	P Value Adjusted for Age (***=Unadjusted for Age)	Age <40	Age ≥40
Systolic Blood Pressure	Officer		0.560	0.746
	Flying Enlisted	0.731		
	Ground Enlisted		0.499	0.701
Diastolic Blood Pressure	Officer		Sparse	0.739
	Flying Enlisted	0.313		
	Ground Enlisted		0.567	0.214
ECG	Officer	0.858		
	Flying Enlisted	0.209		
	Ground Enlisted	0.450		
Heart Sounds	Officer	0.397***		
	Flying Enlisted	0.395***		
	Ground Enlisted		0.255	0.638

Table XVI-1-21 (Cont'd)

SUMMARY OF EXPOSURE INDEX ANALYSES WITHIN THE RANCH HAND GROUP[1]

Dependent Variable**	Occupation	P Value		
		Adjusted for Age (***=Unadjusted for Age)	Age <40	Age ≥40
Eyegrounds	Officer	0.513		
	Flying Enlisted	0.395***		
	Ground Enlisted		0.255	0.638
Carotid Bruits	Officer	0.616		
	Flying Enlisted	0.992		
	Ground Enlisted	0.094		
Popliteal Pulse	Officer	Sparse		
	Flying Enlisted	Sparse		
	Ground Enlisted	0.814		
Dorsalis Pedis Pulse	Officer	0.288		
	Flying Enlisted	0.719		
	Ground Enlisted	0.531		
Posterior Tibial Pulse	Officer	0.643		
	Flying Enlisted	Sparse		
	Ground Enlisted	0.654		
All Pulses	Officer	0.305		
	Flying Enlisted	0.624		
	Ground Enlisted	0.624		
Peripheral Pulses	Officer	0.338		
	Flying Enlisted	0.784		
	Ground Enlisted	0.746		
Leg Pulses	Officer	0.350		
	Flying Enlisted	0.784		
	Ground Enlisted	0.882		

*Peripheral edema omitted for peripheral pulse analyses
**Radial and femoral pulses omitted; data too sparse
***Unadjusted for age.

The data in Table XVI-1-21 clearly indicate that there is no detectable association between the herbicide exposure index adjusted by occupational category and any of the cardiovascular variables.

6. Summary

Central cardiovascular system abnormalities, as manifested by elevated systolic or diastolic blood pressure, abnormal ECG's, and abnormal heart sounds, showed no statistically significant Ranch Hand - comparison group differences, but did reflect a strong correlation to increased age and, to a lesser degree, heavy past smoking. The 3 risk factors of age, smoking, and cholesterol were strongly associated with each other. Unadjusted analyses of Blacks were essentially negative. The prevalence of funduscopic abnormalities and carotid bruits was not associated with group membership but was significantly dependent upon age.

Abnormal peripheral pulses were associated with the Ranch Hand group. A series of detailed covariate analyses showed that pulse abnormalities, regardless of group membership, were associated with increased age (≥ 40 years), heavy past smoking, current smoking, and a verified history of past cardiovascular disease. Substantial Ranch Hand pulse abnormalities were also found in members without prior cardiovascular disease. All significant or borderline significant pulse findings in the Ranch Handers were largely sustained regardless of the comparison group used (originals, matched originals, or all comparisons). Both the femoral and carotid pulses revealed substantial, but statistically nonsignificant, abnormalities in the Ranch Hand group. More biologic credence is assigned to the large artery observations in light of the small artery findings. Peripheral pulse abnormalities will merit extensive clinical inquiry at the first follow-up examination. The history of cardiovascular disease obtained during the in-home interview was verified by a review of medical records. Both reported and verified past heart disease and heart attacks were adjusted by age, smoking, and body fat or HDL. This analysis revealed that the older (≥ 40 years) smoking Ranch Handers manifested significantly more verified heart disease than their equivalent comparisons. Alternatively, the older less smoking Ranch Handers have substantially less reported and verified cardiovascular disease than their comparisons. Detailed herbicide exposure analyses showed no associations to any of the central or peripheral cardiovascular findings. Future reports will explore a theoretical synergism between cigarette smoking and herbicide exposure.